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(54) Title: T-CELL EPITOPES IN ERYTHROPOIETIN

(57) Abstract: The invention relates to the identification of epitopes for T-cells in human EPO as well as T-cell epitope peptides derived from EPO by means of which it is possible to create novel modified EPO variants with reduced immunogenicity.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/505 C12N15/12 A61K38/18 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C12N G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, SEQUENCE SEARCH, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 34317 A (ADAIR FIONA SUZANNE ;CARR FRANCIS JOSEPH (GB); HAMILTON ANITA ANNE) 15 June 2000 (2000-06-15) cited in the application page 8 -page 9; claims 14,21-23 ----	1-5, 8-10, 16-20
X	EP 0 357 804 A (GENETICS INST) 14 March 1990 (1990-03-14) cited in the application column 3; claims 1-9 ----	1-5, 8-10, 16-18
X	EP 0 410 246 A (BEHRINGWERKE AG) 30 January 1991 (1991-01-30) EPO-Peptide P1; page 2, line 50 -page 4, line 26; claims 15-17 ----- -/--	11-15,18

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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5 April 2004

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Name and mailing address of the ISA

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 539 167 A (ORTHO PHARMA CORP) 28 April 1993 (1993-04-28) the whole document ---	
A	EP 1 013 288 A (PFIZER PROD INC) 28 June 2000 (2000-06-28) page 2 -page 3; figures 1-3 ---	
A	EP 0 267 678 A (INTEGRATED GENETICS INC) 18 May 1988 (1988-05-18) pages 2 and 9; figure 4 ---	
A	WO 02 20034 A (BRADBURN JAMES A ;HUNTER CHRISTIE L (US); BOTTI PAOLO (US); CHEN) 14 March 2002 (2002-03-14) Segment SEP-3:4; page 54, line 27 -page 56; example 5 ---	
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P,X	WO 02 069232 A (MERCK PATENT GMBH ;CARTER GRAHAM (GB); JONES TIM (GB); CARR FRANCI) 6 September 2002 (2002-09-06) page 1 -page 11; claims 1,2; example 7 -----	1-10, 16-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08725

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-6,8-10,16-18 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6,8-10,16-18 (all partially)

Present claims 1-5,8-10 and 16-18 relate to a compound defined by reference to a desirable property, namely having the biological activity of human EPO and being substantially non-immunogenic or less immunogenic than any non-modified EPO molecule.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved.

Moreover, present claims 1-5,8-10 and 16-18 relate to a compound defined (inter alia) by reference to the parameter "stimulation index". The use of this parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Furthermore, it is completely unclear in the sense of Article 6 PCT how the following disclaimer is to be understood: "and whereby simultaneously X1=I, X2=L, X3=W, X4=L, X5=L, X6=V, X7=I, X8=F, X9=V, X10=Y, X11=F, X12=L, and X13=L are excluded" (see claim 6). These amino acids are not comprised in the definitions for X1 to X13 in the characterizing part of claim 6, rendering the scope of claims 6 and 8-10 unclear.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the molecules having an amino acid sequence as defined in claim 6 without the disclaimed sequences, and claim 7.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10,16,17 (completely) and 18 (partially)

Modified molecule having the biological activity of human EPO and being substantially non-immunogenic or less immunogenic than any non-modified molecule, DNA coding for such a protein and pharmaceutical composition comprising modified EPO molecules

2. Claims: 11-15,19,20 (completely) and 18 (partially)

Peptide sequence being part of a molecule having the biological activity of human EPO and comprising one or more T-cell epitopes being MHC class II ligands and DNA coding for such a peptide; method of constructing a T-cell epitope map of human EPO by locating T-cell epitopes in human EPO

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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(72) Inventors; and

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